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NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS 4	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS 5	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 6	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS 7	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 8	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 9	JAN 30	Saved answer limit increased
NEWS 10	JAN 31	Monthly current-awareness alert (SDI) frequency added to TULSA
NEWS 11	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 12	FEB 22	Status of current WO (PCT) information on STN
NEWS 13	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 14	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 15	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 16	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS 17	FEB 28	TOXCENTER reloaded with enhancements
NEWS 18	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS 19	MAR 01	INSPEC reloaded and enhanced
NEWS 20	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 21	MAR 08	X.25 communication option no longer available after June 2006
NEWS 22	MAR 22	EMBASE is now updated on a daily basis

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
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FILE 'HOME' ENTERED AT 13:59:32 ON 27 MAR 2006

=> FIL MEDLINE BIOSIS CA EMBASE SCISEARCH
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.42       0.42

FILE 'MEDLINE' ENTERED AT 14:00:35 ON 27 MAR 2006

FILE 'BIOSIS' ENTERED AT 14:00:35 ON 27 MAR 2006
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FILE 'SCISEARCH' ENTERED AT 14:00:35 ON 27 MAR 2006
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=> s (egr (n) 1) or egr1 or TIS8 or (tis (n) 1) or G0S30 or ngfia or (NGFI (n) A)
or KROX24 or (krox (n) 24) or ZIF268 or (zif (n) 268)
L1       13946 (EGR (N) 1) OR EGR1 OR TIS8 OR (TIS (N) 1) OR G0S30 OR NGFIA OR
               (NGFI (N) A) OR KROX24 OR (KROX (N) 24) OR ZIF268 OR (ZIF (N)
              268)

=> s (enzymati? nucle? acid?) or (catalyt? RNA) or (enzymat? RNA) or (catalytic
DNA) or (enzymat? nuclei? acid) or ribozym? or (catalyt? oligonucleoti?) or
nucleozym? or DNAzyme or (RNA enzyme) or oligozyme or (DNA enzyme)
L2       31541 (ENZYMATI? NUCLE? ACID?) OR (CATALYT? RNA) OR (ENZYMAT? RNA) OR
               (CATALYTIC DNA) OR (ENZYMAT? NUCLEI? ACID) OR RIBOZYM? OR (CATAL
              YT? OLIGONUCLEOTI?) OR NUCLEOZYM? OR DNAZYME OR (RNA ENZYME) OR
              OLIGOZYME OR (DNA ENZYME)

=> s l1 and l2
L3         101 L1 AND L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4          57 DUP REM L3 (44 DUPLICATES REMOVED)

=> s l3 and py<=1999
   1 FILES SEARCHED...
L5          13 L3 AND PY<=1999

=> s ATKINS, D?/au;s BAKER, A?/au;s KHACHIGIAN, L?/au
L6        1286 ATKINS, D?/AU


L7        8316 BAKER, A?/AU


L8         536 KHACHIGIAN, L?/AU

=> s l6 or l7 or l8
L9       10108 L6 OR L7 OR L8

=> s l9 and l1
L10        200 L9 AND L1
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=> dup rem l10
PROCESSING COMPLETED FOR L10
L11 67 DUP REM L10 (133 DUPLICATES REMOVED)

=> s l11 and l2
L12 24 L11 AND L2

=> s l12 or l5
L13 32 L12 OR L5

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14 27 DUP REM L13 (5 DUPLICATES REMOVED)

=> s l14 ibib abs 1-27
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=> d l14 ibib abs 1-27

L14 ANSWER 1 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:163870 BIOSIS
DOCUMENT NUMBER: PREV200600177956
TITLE: **DNAzymes** targeting immediate-early genes as inhibitors of angiogenesis and restenosis.
AUTHOR(S): **Khachigian, Levon M.** [Reprint Author]
CORPORATE SOURCE: Univ New S Wales, Ctr Vasc Res, Sydney, NSW, Australia
SOURCE: **Khachigian, LM** [Editor]. (2005) pp. 153-159.
SYNTHETIC NUCLEIC ACIDS AS INHIBITORS OF GENE EXPRESSION: MECHANISMS, APPLICATIONS, AND THERAPEUTIC IMPLICATIONS.
Publisher: CRC PRESS-TAYLOR & FRANCIS GROUP, 6000 BROKEN SOUND PARKWAY NW, STE 300, BOCA RATON, FL 33487-2742 USA.
ISBN: 0-8493-3025-4(H).
DOCUMENT TYPE: Book; (Book Chapter)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Mar 2006
Last Updated on STN: 9 Mar 2006

L14 ANSWER 2 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:58610 BIOSIS
DOCUMENT NUMBER: PREV200600046887
TITLE: **DNAzymes** targeting the transcription factor **Egr-1** reduce myocardial infarct size following ischemia-reperfusion in rats.
AUTHOR(S): Bhindi, Ravinay [Reprint Author]; **Khachigian, Levon M.**; Lowe, Harry C.
CORPORATE SOURCE: Univ New S Wales, Sydney, NSW, Australia
SOURCE: Circulation, (OCT 25 2005) Vol. 112, No. 17, Suppl. S, pp. U239.
Meeting Info.: 78th Annual Scientific Session of the American-Heart-Association. Dallas, TX, USA. November 13 -16, 2005. Amer Heart Assoc.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jan 2006
Last Updated on STN: 4 Jan 2006

L14 ANSWER 3 OF 27 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 142:422680 CA
TITLE: **DNAzymes** targeting immediate-early genes as inhibitors of angiogenesis and restenosis

AUTHOR(S): **Khachigian, Levon M.**
CORPORATE SOURCE: Centre for Vascular Research, University of New South Wales, Sydney, Australia
SOURCE: Synthetic Nucleic Acids as Inhibitors of Gene Expression (2005), 153-159,, 2 plates. Editor(s): **Khachigian, Levon Michael**. CRC Press LLC: Boca Raton, Fla.
CODEN: 69GHNX; ISBN: 0-8493-3025-4
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review focuses on early growth response-**1** (**Egr-1**) and the basic region-leucine zipper protein c-Jun **DNAzymes**.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2004467383 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15247255
TITLE: Fibroblast growth factor-2 induction of platelet-derived growth factor-C chain transcription in vascular smooth muscle cells is ERK-dependent but not JNK-dependent and mediated by **Egr-1**.
AUTHOR: Midgley Valerie C; **Khachigian Levon M**
CORPORATE SOURCE: Centre for Vascular Research, The University of New South Wales, Department of Haematology, The Prince of Wales Hospital, Sydney, New South Wales 2052, Australia.
SOURCE: The Journal of biological chemistry, (2004 Sep 24) Vol. 279, No. 39, pp. 40289-95. Electronic Publication: 2004-07-09.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 20040921
Last Updated on STN: 20041027
Entered Medline: 20041026
AB Platelet-derived growth factors (PDGFs) play an integral role in normal tissue growth and maintenance as well as many human pathological states including atherosclerosis, fibrosis, and tumorigenesis. The PDGF family of ligands is comprised of A, B, C, and D chains. Here, we provide the first functional characterization of the PDGF-C promoter. We examined 797 bp of the human PDGF-C promoter and identified several putative recognition elements for Sp1, Ets **Egr-1**, and Smad.
The proximal region of the PDGF-C promoter bears a remarkable resemblance to a comparable region of the PDGF-A promoter (1). Binding and transient transfection analysis in primary vascular smooth muscle cells revealed that PDGF-C, like PDGF-A, is under the transcriptional control of the zinc finger nuclear protein **Egr-1** (early growth response-1). Electrophoretic mobility shift analysis using both smooth muscle cell nuclear extracts and recombinant protein revealed that **Egr-1** and Sp1 bind this region of the PDGF-C promoter (Oligo C, -35 to -1). **Egr-1** competes with Sp1 for overlapping binding sites even when the former is at a stoichiometric disadvantage. Reverse transcriptase PCR and supershift analysis demonstrate that fibroblast growth factor-2 (FGF-2) stimulates both **Egr-1** and PDGF-C mRNA expression in a time-dependent and transient manner and that FGF-2-inducible **Egr-1** binds the proximal PDGF-C promoter. FGF-2-inducible PDGF-C expression was completely abrogated using **catalytic DNA** (**DNAzymes**) targeting **Egr-1** but not by its scrambled counterpart. Moreover, using pharmacological inhibitors we

demonstrate the critical role of ERK but not JNK in FGF-2-inducible PDGF-C expression. These findings thus demonstrate that PDGF-C transcription, activated by FGF-2, is mediated by **Egr-1** and its upstream kinase ERK.

L14 ANSWER 5 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2004281559 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15181171
TITLE: Inhibition of human breast carcinoma proliferation, migration, chemoinvasion and solid tumour growth by **DNAzymes** targeting the zinc finger transcription factor **EGR-1**.
AUTHOR: Mitchell Ainslie; Dass Crispin R; Sun Lun-Quan; **Khachigian Levon M**
CORPORATE SOURCE: Department of Haematology, Centre for Vascular Research, The University of New South Wales, Sydney, NSW 2052, Australia.
SOURCE: Nucleic acids research, (2004) Vol. 32, No. 10, pp. 3065-9. Electronic Publication: 2004-06-04. Journal code: 0411011. E-ISSN: 1362-4962.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20040608
Last Updated on STN: 20040625
Entered Medline: 20040624

AB **DNAzymes** (synthetic **catalytic DNA**) have emerged as a new class of nucleic acid-based gene silencing agent. Using **DNAzymes** targeting the human mRNA of the immediate-early gene and C2H2-class zinc finger transcription factor early growth response-**1** (**EGR-1**), we demonstrate here that **EGR-1** plays an indispensable role in breast cancer proliferation, migration, chemoinvasion and xenograft growth in nude mice. **DNAzyme** inhibition of these tumorigenic processes and **EGR-1** protein expression in breast carcinoma cells is sequence-specific and **EGR-1** transcription-independent. These agents inhibit breast carcinoma cell migration and chemoinvasion in microchemotaxis chambers and solid tumour growth in athymic nude mice. Thus, **DNAzymes** targeting specific genes can inhibit multiple key tumorigenic processes in vitro and in vivo and may serve as useful anti-cancer agents.

L14 ANSWER 6 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2004210327 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15107496
TITLE: Locked nucleic acid modified **DNA enzymes** targeting early growth response-1 inhibit human vascular smooth muscle cell growth.
AUTHOR: Fahmy Roger G; **Khachigian Levon M**
CORPORATE SOURCE: Centre for Vascular Research, Department of Pathology, The University of New South Wales and Department of Haematology, Prince of Wales Hospital, Sydney, Australia.
SOURCE: Nucleic acids research, (2004) Vol. 32, No. 7, pp. 2281-5. Electronic Publication: 2004-04-23. Journal code: 0411011. E-ISSN: 1362-4962.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405

ENTRY DATE: Entered STN: 20040427
Last Updated on STN: 20040512
Entered Medline: 20040511

AB Smooth muscle cell (SMC) proliferation and migration are key processes that occur in the pathogenesis of atherosclerosis and post-angioplasty restenosis. In the present study, we designed locked nucleic acid (LNA)-modified **DNAzymes** targeting a specific region spanning the translational start site of human **EGR-1**, an immediate-early gene, wherein two of the nucleotides in each of the 9+9 hybridizing arms of the **DNAzyme** were substituted with LNA monomers. In vitro cleavage experiments revealed that the LNA- modified **DNAzyme** (LzF4) cleaved a 32P-labelled 388 nt **EGR-1** transcript with greater efficacy than its native unmodified phosphodiester counterpart, DzF. The scrambled versions of these molecules, LzF4SCR and DzFSCR, did not display any ability to cleave the transcript. Western blot analysis revealed that both active molecules abrogated serum-inducible **EGR-1** protein expression in primary human aortic SMCs and inhibited serum-inducible SMC proliferation in a dose-dependent and non-toxic manner. SMC proliferation was inhibited by >50% with LzF4 at concentrations as low as 20 nM, whereas inhibition by DzF at this concentration was not evident. Finally, LzF4 and DzF inhibited SMC regrówth from the wound edge after mechanical injury in vitro. In contrast, neither DzFSCR nor LzF4SCR had any influence on **EGR-1** protein expression, SMC proliferation or regrowth. These findings provide the first functional demonstration of LNA-modified **DNAzyme** efficacy in a biological setting of any kind. These studies also demonstrate that LNA modification increases **DNAzyme** potency without necessarily compromising specificity.

L14 ANSWER 7 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2004407948 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15313396
TITLE: **DNAzymes** as molecular agents that manipulate **Egr-1** gene expression.
AUTHOR: **Khachigian Levon M**
CORPORATE SOURCE: Department of Haematology, Centre for Vascular Research, University of New South Wales, Prince of Wales Hospital, Sydney, Australia.. l.khachigian@unsw.edu.au
SOURCE: Biochemical pharmacology, (2004 Sep 15) Vol. 68, No. 6, pp. 1023-5. Ref: 23
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20040818
Last Updated on STN: 20040928
Entered Medline: 20040927

AB In recent years, the arsenal of small-molecule synthetic nucleic acids as gene-specific "knock-down" agents has increased in scope and variety. The investigator has the choice of antisense oligonucleotides, **ribozymes**, siRNA and **DNAzymes**, each subclass further benefiting from modifications that increase stability and efficiency and decrease toxicity. This review describes our use of **DNAzymes** in efforts to define the roles of key transcription factor targets, first in cultured vascular cells, then in animal models of neovascularization and arterial thickening.

L14 ANSWER 8 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:918298 SCISEARCH
THE GENUINE ARTICLE: 859XX

TITLE: Deoxyribozymes as inhibitors of vascular smooth muscle cell growth
AUTHOR: **Khachigian L M (Reprint)**
CORPORATE SOURCE: Univ New S Wales, Ctr Vasc Res, Sydney, NSW 2052, Australia (Reprint); Prince Wales Hosp, Dept Haematol, Sydney, NSW, Australia
L.Khachigian@unsw.edu.au
COUNTRY OF AUTHOR: Australia
SOURCE: CURRENT PHARMACEUTICAL BIOTECHNOLOGY, (AUG 2004) Vol. 5, No. 4, pp. 337-339.
ISSN: 1389-2010.
PUBLISHER: BENTHAM SCIENCE PUBL LTD, EXECUTIVE STE Y26, PO BOX 7917, SAIF ZONE, 1200 BR SHARJAH, U ARAB EMIRATES.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 19
ENTRY DATE: Entered STN: 11 Nov 2004
Last Updated on STN: 11 Nov 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **DNA enzymes**, or **DNAzymes**, are all-DNA molecules with inherent catalytic activity that bind and cleave at their complementary sequence in the target mRNA through Watson-Crick base pairing. These agents have been successfully used to tease out the role the targeted gene plays in both cellular systems and in a variety of animal models. **DNAzymes** have the potential to serve as novel nucleic acid-based therapeutic agents in pathologies involving aberrant smooth muscle cell growth and a range of other disorders.

L14 ANSWER 9 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2003576609 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14657654
TITLE: Early growth response-1: blocking angiogenesis by shooting the messenger.
AUTHOR: **Khachigian Levon M**
CORPORATE SOURCE: Centre for Vascular Research, Department of Pathology, University of New South Wales, Sydney, NSW 2052, Australia.. L.Khachigian@unsw.edu.au
SOURCE: Cell cycle (Georgetown, Tex.), (2004 Jan) Vol. 3, No. 1, pp. 10-1. Ref: 7
Journal code: 101137841. ISSN: 1538-4101.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040618
Entered Medline: 20040617

AB Early growth response-**1** (**Egr-1**) is an immediate early gene, which encodes a zinc finger transcription factor. Recent evidence indicates that **Egr-1** plays a crucial role in angiogenesis, the formation of new blood vessels from the pre-existing vasculature. **DNAzymes** (catalytic single-stranded DNA) targeting the **Egr-1** mRNA inhibit **Egr-1** and FGF-2 expression, block endothelial cell growth, and suppress neovascularization and tumor angiogenesis in various animal models.

L14 ANSWER 10 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2003361085 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12872165
TITLE: Transcription factor **Egr-1** supports FGF-dependent angiogenesis during neovascularization and

tumor growth.
AUTHOR: Fahmy Roger G; Dass Crispin R; Sun Lun-Quan; Chesterman Colin N; **Khachigian Levon M**
CORPORATE SOURCE: Centre for Vascular Research, University of New South Wales, Sydney NSW 2052, Australia.
SOURCE: Nature medicine, (2003 Aug) Vol. 9, No. 8, pp. 1026-32. Electronic Publication: 2003-07-20. Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030802
Last Updated on STN: 20031001
Entered Medline: 20030930

AB Current understanding of key transcription factors regulating angiogenesis is limited. Here we show that RNA-cleaving phosphodiester-linked DNA-based enzymes (**DNAzymes**), targeting a specific motif in the 5' untranslated region of early growth response (**Egr-1**) mRNA, inhibit **Egr-1** protein expression, microvascular endothelial cell replication and migration, and microtubule network formation on basement membrane matrices. **Egr-1** **DNAzymes** blocked angiogenesis in subcutaneous Matrigel plugs in mice, an observation that was independently confirmed by plug analysis in **Egr-1**-deficient animals, and inhibited MCF-7 human breast carcinoma growth in nude mice. **Egr-1** **DNAzymes** suppressed tumor growth without influencing body weight, wound healing, blood coagulation or other hematological parameters. These agents inhibited endothelial expression of fibroblast growth factor (FGF)-2, a proangiogenic factor downstream of **Egr-1**, but not that of vascular endothelial growth factor (VEGF). **Egr-1** **DNAzymes** also repressed neovascularization of rat cornea. Thus, microvascular endothelial cell growth, neovascularization, tumor angiogenesis and tumor growth are processes that are critically dependent on **Egr-1**.

L14 ANSWER 11 OF 27 EMBASE
ACCESSION NUMBER: 2002216432 EMBASE
TITLE: **DNAzymes**: Cutting a path to a new class of therapeutics.
AUTHOR: **Khachigian L.M.**
CORPORATE SOURCE: L.M. Khachigian, Centre for Thrombosis/Vascular Res., Department of Pathology, University of New South Wales, Sydney, NSW 2052, Australia. L.Khachigian@unsw.edu.au
SOURCE: Current Opinion in Molecular Therapeutics, (2002) Vol. 4, No. 2, pp. 119-121. .
Refs: 34
ISSN: 1464-8431 CODEN: CUOTFO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020708
Last Updated on STN: 20020708

AB **DNAzymes** are synthetic catalytic deoxyribonucleic acid molecules that can be engineered to bind to their complementary sequence in the target nucleic acid through Watson-Crick base pairing and cleave at predetermined phosphodiester linkages. This article reviews the recent

use of **DNAzymes** as probes of molecular function and their potential applications in clinical medicine.

L14 ANSWER 12 OF 27 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 134:344560 CA
TITLE: Sequences of antisense oligonucleotides and **catalytic DNA** targeting **Egr** -**1** mRNA and uses thereof in cancer therapy
INVENTOR(S): **Khachigian, Levon Michael**
PATENT ASSIGNEE(S): Unisearch Ltd., Australia
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030394	A1	20010503	WO 2000-AU1315	20001026
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2388998	AA	20010503	CA 2000-2388998	20001026
AU 2001011169	A5	20010508	AU 2001-11169	20001026
EP 1225919	A1	20020731	EP 2000-972446	20001026
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003512442	T2	20030402	JP 2001-532811	20001026
ZA 2002003166	A	20030422	ZA 2002-3166	20020422
US 2003203864	A1	20031030	US 2002-133226	20020426

PRIORITY APPLN. INFO.:		
AU 1999-3676	A	19991026
WO 2000-AU1315	W	20001026
US 2002-133226	A	20020426

AB The present invention relates to a method for the treatment of tumors, the method comprising inhibiting angiogenesis in a subject in need thereof characterized in that angiogenesis is inhibited by administering to the subject an agent which inhibits induction of EGR, an agent which decreases expression of EGR or an agent which decreases the nuclear accumulation or activity of EGR. The present invention also relates to a method of screening for agents which inhibits angiogenesis. In particular, the invention provides sequences of antisense oligonucleotides and **catalytic DNA** targeting **EGR**-**1** mRNA and their uses in cancer therapy.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:138633 BIOSIS
DOCUMENT NUMBER: PREV200200138633
TITLE: **Catalytic oligonucleotides** targeting **EGR**-**1** as potential inhibitors of in-stent restenosis.
AUTHOR(S): **Khachigian, Levon M.** [Reprint author]
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, University of New South Wales, Sydney, NSW, 2052, Australia
L.Khachigian@unsw.edu.au

SOURCE: Numano, Fujio [Editor]; Gimbrome, Michael A., Jr. [Editor]. Ann. N. Y. Acad. Sci., (2001) pp. 412-415. Annals of the New York Academy of Sciences. Atherosclerosis VI: The sixth Saratoga international conference. print.
Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: Annals of the New York Academy of Sciences.
Meeting Info.: Sixth Saratoga International Conference on Atherosclerosis. Tokyo, Japan. April 03-06, 2001.
CODEN: ANYAA9. ISSN: 0077-8923. ISBN: 1-57331-364-5 (cloth), 1-57331-365-3 (paper).

DOCUMENT TYPE: Book
Conference; (Meeting)
Book; (Book Chapter)
Conference; (Meeting Paper)

LANGUAGE: English

ENTRY DATE: Entered STN: 6 Feb 2002
Last Updated on STN: 26 Feb 2002

L14 ANSWER 14 OF 27 MEDLINE on STN

ACCESSION NUMBER: 2001551213 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11597989

TITLE: Catalytic oligodeoxynucleotides define a key regulatory role for early growth response factor-1 in the porcine model of coronary in-stent restenosis.

AUTHOR: Lowe H C; Fahmy R G; Kavurma M M; **Baker A**; Chesterman C N; **Khachigian L M**

CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, University of New South Wales and Prince of Wales Hospital, Sydney, Australia.

SOURCE: Circulation research, (2001 Oct 12) Vol. 89, No. 8, pp. 670-7.
Journal code: 0047103. E-ISSN: 1524-4571.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200110

ENTRY DATE: Entered STN: 20011015
Last Updated on STN: 20011029
Entered Medline: 20011025

AB Early growth response factor-**1** (**Egr-1**) controls the expression of a growing number of genes involved in the pathogenesis of atherosclerosis and postangioplasty restenosis. **Egr-1** is activated by diverse proatherogenic stimuli. As such, this transcription factor represents a key molecular target in efforts to control vascular lesion formation in humans. In this study, we have generated **DNAzymes** targeting specific sequences in human **EGR-1** mRNA. These molecules cleave in vitro transcribed **EGR-1** mRNA efficiently at preselected sites, inhibit **EGR-1** protein expression in human aortic smooth muscle cells, block serum-inducible cell proliferation, and abrogate cellular regrowth after mechanical injury in vitro. These **DNAzymes** also selectively inhibit **EGR-1** expression and proliferation of porcine arterial smooth muscle cells and reduce intimal thickening after stenting pig coronary arteries in vivo. These findings demonstrate that endoluminally delivered **DNAzymes** targeting **EGR-1** may serve as inhibitors of in-stent restenosis.

L14 ANSWER 15 OF 27 MEDLINE on STN

ACCESSION NUMBER: 2002069980 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11795303

TITLE: **Catalytic oligonucleotides** targeting **EGR-1** as potential inhibitors of in-stent

restenosis.
AUTHOR: **Khachigian L M**
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, The University of New South Wales, Sydney, Australia..
L.Khachigian@unsw.edu.au
SOURCE: Annals of the New York Academy of Sciences, (2001 Dec) Vol. 947, pp. 412-5. Ref: 33
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020202
Entered Medline: 20020201

AB This brief review discusses recent strategies targeting the zinc finger transcription factor and immediate-early gene product **Egr-1** with **catalytic DNA** in efforts to inhibit postangioplasty restenosis.

L14 ANSWER 16 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:274949 BIOSIS
DOCUMENT NUMBER: PREV200200274949
TITLE: Catalytic oligodeoxynucleotides targeting the human transcription factor **Egr-1** as inhibitors of restenosis.
AUTHOR(S): Lowe, Harry Claude [Reprint author]; Fahmy, Roger [Reprint author]; Chesterman, Colin N. [Reprint author]; **Khachigian, Levon M.** [Reprint author]
CORPORATE SOURCE: Ctr for Thrombosis and Vascular Research, Sydney, NSW, Australia
SOURCE: Circulation, (October 23, 2001) Vol. 104, No. 17 Supplement, pp. II.265. print.
Meeting Info.: Scientific Sessions 2001 of the American Heart Association. Anaheim, California, USA. November 11-14, 2001. American Heart Association.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 May 2002
Last Updated on STN: 8 May 2002

L14 ANSWER 17 OF 27 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 133:116709 CA
TITLE: **Catalytic DNA** targeted to **EGR-1** mRNA and their therapeutic use
INVENTOR(S): **Atkins, David G.; Baker, Andrew R. ; Khachigian, Levon Michael**
PATENT ASSIGNEE(S): Unisearch Limited, Australia; Johnson & Johnson Research Pty. Ltd.
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000042173	A1	20000720	WO 2000-AU11	20000111

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2360387	AA	20000720	CA 2000-2360387		20000111
EP 1151089	A1	20011107	EP 2000-902488		20000111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002534117	T2	20021015	JP 2000-593730		20000111
NZ 512805	A	20030725	NZ 2000-512805		20000111
PRIORITY APPLN. INFO.:			AU 1999-8103	A	19990111
			WO 2000-AU11	W	20000111

AB The present invention relates to **DNAzymes** which are targeted against mRNA mols. encoding **EGR-1** (also known as **Egr-1** or **NGFI-A**). The present invention also relates to compns. including these **DNAzymes** and to methods of treatment involving administration of the **DNAzymes**. Thus, a **DNAzyme** binding to bp 189-207 of human **EGR-1** mRNA and cleaving the 198G-199U bond blocked induction of **EGR-1** and inhibited growth of human smooth muscle cells.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 18 OF 27 MEDLINE on STN

ACCESSION NUMBER: 2001090066 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11086018
TITLE: **Catalytic DNAs** as potential therapeutic agents and sequence-specific molecular tools to dissect biological function.
AUTHOR: **Khachigian L M**
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, School of Pathology, The University of New South Wales, Sydney, Australia.. L.Khachigian@unsw.edu.au
SOURCE: The Journal of clinical investigation, (2000 Nov) Vol. 106, No. 10, pp. 1189-95. Ref: 50
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010125

L14 ANSWER 19 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:164698 BIOSIS
DOCUMENT NUMBER: PREV200000164698
TITLE: A novel **catalytic DNA** molecule targeting the transcription factor **Egr-1** inhibits neointimal formation following rat carotid angioplasty.
AUTHOR(S): Lowe, H. C. [Reprint author]; Santiago, F. S. [Reprint author]; Chesterman, C. N. [Reprint author]; **Khachigian, L. M.** [Reprint author]
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, University of New South Wales, Sydney, NSW, Australia

SOURCE: Journal of the American College of Cardiology, (Feb., 2000) Vol. 35, No. 2 suppl. A, pp. 15A. print.
Meeting Info.: 29th Annual Scientific Session of the American College of Cardiology. Anaheim, California, USA. March 12-15, 2000.
CODEN: JACCDI. ISSN: 0735-1097.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Apr 2000
Last Updated on STN: 4 Jan 2002

L14 ANSWER 20 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2000095809 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10636800
TITLE: DNA cuts its teeth--as an enzyme.
AUTHOR: Finkel E
SOURCE: Science, **(1999 Dec 24)** Vol. 286, No. 5449, pp. 2441-2.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: News Announcement
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000111

L14 ANSWER 21 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:156467 BIOSIS
DOCUMENT NUMBER: PREV200000156467
TITLE: DNA cuts its teeth-as an enzyme.
AUTHOR(S): Finkel, Elizabeth
SOURCE: Science (Washington D C), (**Dec. 24, 1999**) Vol. 286, No. 5449, pp. 2441-2442. print.
CODEN: SCIEAS. ISSN: 0036-8075.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Apr 2000
Last Updated on STN: 4 Jan 2002
AB One problem with using angioplasty to treat blocked arteries is the potential for triggering a reactive repair process that itself can clog the artery. Researcher Levon Khachigian at the University of New South Wales, Australia and his colleagues have reported promising results with an enzyme made from DNA that might inactivate the damage-sensing gene called **Egr-1**.

L14 ANSWER 22 OF 27 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 132:179042 CA
TITLE: New **DNA enzyme** targeting **Egr-1** mRNA inhibits vascular smooth muscle proliferation and regrowth after injury. [Erratum to document cited in CA132:48454]
AUTHOR(S): Santiago, Fernando S.; Lowe, Harry C.; Kavurma, Mary M.; Chesterman, Colin N.; **Baker, Andrew**; **Atkins, David G.**; **Khachigian, Levon M.**
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, The Univ. New South Wales and Prince of Wales Hospital, Sydney, Australia
SOURCE: Nature Medicine (New York) (**1999**), 5(12), 1438

CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB On page 1264 in the paragraph beginning "To determine whether...", the corrected
second and third sentences are given: "ED5 cleaved this 23-nucleotide substrate (labeled with 32P at the 5' end) within 10 min (Fig. 1b). The 12-nucleotide product (Fig. 1b) is consistent with the length between the A816-U817 junction and the 5' (radiolabeled) end of the substrate (Fig. 1a).".

L14 ANSWER 23 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1999426554 EMBASE
TITLE: Erratum: New **DNA enzyme** targeting **Egr-1** mRNA inhibits vascular smooth muscle proliferation and regrowth after injury (Nature Medicine (1999) 5 (1264-1269)).
AUTHOR: Santiago F.S.; Lowe H.C.; Kavurma M.M.; Chesterman C.N.; **Baker A.**; **Atkins D.G.**; **Khachigian L.M.**
SOURCE: Nature Medicine, (1999) Vol. 5, No. 12, pp. 1438. . ISSN: 1078-8956 CODEN: NAMEFI
COUNTRY: United States
DOCUMENT TYPE: Journal; Errata
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
ENTRY DATE: Entered STN: 19991229
Last Updated on STN: 19991229
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L14 ANSWER 24 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:934380 SCISEARCH
THE GENUINE ARTICLE: 262DE
TITLE: New **DNA enzyme** targeting **Egr -1** mRNA inhibits vascular smooth muscle proliferation and regrowth after injury (vol 5, pg 1264, 1999)
AUTHOR: Santiago F S (Reprint); Lowe H C; Kavurma M M; Chesterman C N; **Baker A**; **Atkins D G**; **Khachigian L M**
SOURCE: NATURE MEDICINE, (**DEC 1999**) Vol. 5, No. 12, pp. 1438-1438. ISSN: 1078-8956.
PUBLISHER: NATURE AMERICA INC, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707 USA.
DOCUMENT TYPE: Errata; Journal
LANGUAGE: English
REFERENCE COUNT: 1
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999

L14 ANSWER 25 OF 27 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2000015189 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10545992
TITLE: New **DNA enzyme** targeting **Egr-1** mRNA inhibits vascular smooth muscle proliferation and regrowth after injury.
AUTHOR: Santiago F S; Lowe H C; Kavurma M M; Chesterman C N; **Baker A**; **Atkins D G**; **Khachigian L M**
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, The University

of New South Wales and Prince of Wales Hospital, Sydney, Australia.

SOURCE: Nature medicine, **(1999 Nov)** Vol. 5, No. 11, pp. 1264-9.
Journal code: 9502015. ISSN: 1078-8956.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000320
Entered Medline: 19991119

AB Early growth response factor-**1** (**Egr-1**) binds to the promoters of many genes whose products influence cell movement and replication in the artery wall. Here we targeted **Egr-1** using a new class of DNA-based enzyme that specifically cleaved **Egr-1** mRNA, blocked induction of **Egr-1** protein, and inhibited cell proliferation and wound repair in culture. The **DNA enzyme** also inhibited **Egr-1** induction and neointima formation after balloon injury to the rat carotid artery wall. These findings demonstrate the utility of **DNA enzymes** as biological tools to delineate the specific functions of a given gene, and implicate catalytic nucleic acid molecules composed entirely of DNA as potential therapeutic agents.

L14 ANSWER 26 OF 27 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 127:257645 CA
TITLE: Control of **Egr-1** synthesis and activity in inhibition of endothelial cell proliferation in control of restenosis and atherosclerosis
INVENTOR(S): **Khachigian, Levon Michael**
PATENT ASSIGNEE(S): Unisearch Ltd., Australia; Khachigian, Levon Michael
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9732979	A1	19970912	WO 1997-AU140		19970307 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
CA 2248350	AA	19970912	CA 1997-2248350		19970307 <--
AU 9720865	A1	19970922	AU 1997-20865		19970307 <--
AU 707943	B2	19990722			
ZA 9702000	A	19971024	ZA 1997-2000		19970307 <--
EP 934404	A1	19990811	EP 1997-906032		19970307 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2000506725	T2	20000606	JP 1997-531259		19970307
US 6200960	B1	20010313	US 1999-142779		19990413
US 2004072768	A1	20040415	US 2001-757555		20010109
PRIORITY APPLN. INFO.:			AU 1996-8554	A	19960307
			WO 1997-AU140	W	19970307

US 1999-142779 A2 19990413

AB A method of inhibiting proliferation of cells by inhibiting induction or decreasing expression of the **Egr-1** gene or decreasing the nuclear accumulation or activity of the **Egr-1** gene product is described. **Egr-1** is found to be one of the immediate-early genes induced in response to vascular injury and to play a role in restenosis and atherosclerosis. Inhibitors of **Egr-1** expression may include antisense DNA, **ribozymes**, or transcriptional decoys. Antisense oligonucleotides to **Egr-1** were taken by smooth muscle cells in culture without significant degradation and inhibited their proliferation. **Egr-1** protein synthesis was inhibited, but Sp1 synthesis was not.

L14 ANSWER 27 OF 27 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 97434297 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9288183
TITLE: Development of a hammerhead **ribozyme** against bcl-2. I. Preliminary evaluation of a potential gene therapeutic agent for hormone-refractory human prostate cancer.
AUTHOR: Dorai T; Olsson C A; Katz A E; Buttyan R
CORPORATE SOURCE: Department of Urology, College of Physicians and Surgeons of Columbia University, New York, New York 10032, USA.
SOURCE: The Prostate, **(1997 Sep 1)** Vol. 32, No. 4, pp. 246-58.
Journal code: 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971013
Last Updated on STN: 19971013
Entered Medline: 19970930

AB BACKGROUND: The bcl-2 oncoprotein suppresses apoptosis and, when overexpressed in prostate cancer cells, makes these cells resistant to a variety of therapeutic agents, including hormonal ablation. Therefore, bcl-2 provides a strategic target for the development of gene knockout therapies to treat human prostate cancers. Towards this end, we have synthesized an anti-bcl-2 gene therapeutic reagent based on **ribozyme** technology and have tested its effectiveness against bcl-2 mRNA in vitro and in vivo. METHODS: A divalent hammerhead **ribozyme** was constructed by recombining two **catalytic RNA** domains into an antisense segment of the coding region for human bcl-2 mRNA. A disabled **ribozyme** lacking catalytic activity was also constructed as a control reagent for our experiments. The **ribozymes** were tested for endonucleolytic activity against synthetic and natural bcl-2 mRNAs. Simple transfection procedures were then utilized to introduce the **ribozymes** into cultured prostate cancer cells (LNCaP derivatives). We measured the effects of the **ribozymes** on endogenous expression of bcl-2 mRNA and protein in these cells as well as their ability to induce apoptosis. RESULTS: The functional but not the disabled **ribozyme** was able to rapidly degrade bcl-2 mRNA in vitro, without the requirement for any other cellular protein or factor. When directly transfected into LNCaP cell variants, it significantly reduced bcl-2 mRNA and protein levels within 18 hr of treatment. This activity was sufficient to induce apoptosis in a low-bcl-2-expressing variant of LNCaP, but not in a high-bcl-2-expressing LNCaP line. For the high-bcl-2-expressing variant, however, it did restore the ability to genetically respond to a secondary apoptotic agent, phorbol ester, as evidenced by the renewed ability of phorbol ester to induce NGF1A mRNA in these cells. CONCLUSIONS: This study supports the potential utility of an anti-bcl-2 **ribozyme** reagent for reducing or eliminating bcl-2 expression from hormone-refractory prostate cancer

cells and for killing prostate cancer cells. As such, it is the first step toward an effective gene therapy against hormone-refractory human prostate cancers.